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Indole Diterpenoid Synthetic Studies. The Total Synthesis of (+)-Nodulisporic Acid F

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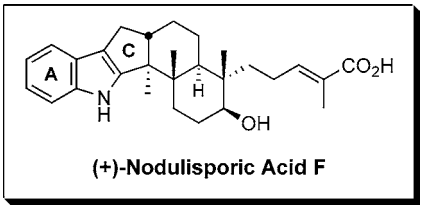
ABSTRACT



(+)-Nodulisporic Acid F

A stereocontrolled total synthesis of (+)-nodulisporic acid F, the simplest member of a family of novel ectoparasiticidal agents, has been achieved. Highlights of the effective modular synthetic strategy include anionic union of a tricyclic lactone with *o*-toluidine via our 2-substituted indole synthetic protocol, an optimized C-ring construction protocol, and a late-stage installation of the α,β-unsaturated carboxylic acid side chain via the *B*-alkyl Suzuki–Miyaura cross-coupling tactic.

(+)-Nodulisporic acid A (**1**; Figure 1), an indole diterpenoid reported by Ondeyka and co-workers in 1997,[1] produced by the endophytic fungus, *Nodulisporium* sp. (MF5954), was reported to be an effective systemic ectoparasiticidal agent against fleas on dogs. The mode of action emanates from modulation of invertebrate-specific glutamate-gated chloride ion channels;[2] thus nodulisporic acid A (**1**) is devoid of mammalian toxicity. Although exhibiting good in vitro and in vivo activity against fleas, the potency and pharmacokinetic profile did not justify direct commercialization. A medicinal chemistry campaign was therefore undertaken by Merck and Co. to optimize the profile of this lead compound. Synthetic efforts focusing on the dienoic acid side chain of the molecule culminated in the synthesis of over 1000 analogues.[3] In parallel with medicinal chemistry efforts, Merck scientists sought congeners and/or natural analogues of the parent compound, both from the original producer as well as variants derived by chemical mutagenesis. The latter effort led to the discovery of nodulisporic acids A_1, A_2, B, B_1, B_2, C, C_1, C_2, as well as putative biosynthetic intermediates nodulisporic acids D (**2**), D_1, D_2, D_3, E, and F (**3**; Figure 1).[4]

Given our long-standing interest in the indole-diterpenoid class of natural products,[5] the nodulisporic acids captured our attention as worthy synthetic targets. From the outset, our ultimate goal was to devise a convergent, *modular* synthetic strategy that would permit access to all of the nodulisporic acids, as well as to an array of unnatural

(1) (a) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809. (b) Ostlind, D. A.; Felcetto, T.; Misura, A.; Ondeyka, J. G.; Smith, S.; Goetz, M.; Shoop, W.; Mickle, W. *Med. Vet. Entomol.* **1997**, *11*, 407.

(2) Ludmerer, S. W.; Warren, V. A.; Williams, B. S.; Zheng, Y. C.; Hunt, D. C.; Ayer, M. B.; Wallace, M. A.; Chaudhary, A. G.; Egan, M. A.; Meinke, P. T.; Dean, D. C.; Garcia, M. L.; Cully, D. F.; Smith, M. M. *Biochemistry* **2002**, *41*, 6548 and references therein.

(3) Chakravarty, P. K.; Shih, T. L.; Colletti, S. L.; Ayer, M. B.; Snedden, C.; Kuo, H.; Tyagarajan, S.; Gregory, L.; Zakson-Aiken, M.; Shoop, W. L.; Schmatz, D. M.; Wyvratt, M. J.; Fisher, M. H.; Meinke, P. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 147 and references therein.

(4) Singh, S. B.; Ondeyka, J. G.; Jayasuriya, H.; Zink, D. L.; Ha, S. N.; Dahl-Roshak, A. M.; Greene, J.; Kim, J. A.; Smith, M. M.; Shoop, W.; Tkacz, J. S. *J. Nat. Prod.* **2004**, *67*, 1496 and references therein.

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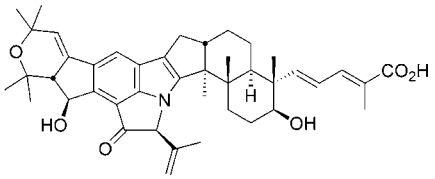
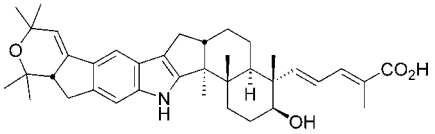


(+)-Nodulisporic Acid A (**1**)



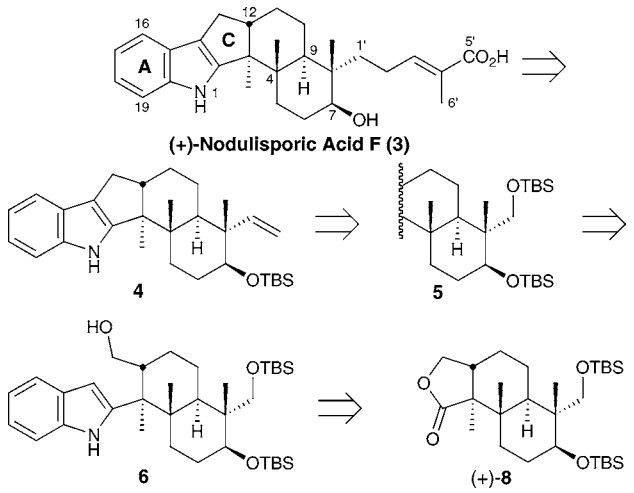
(-)-Nodulisporic Acid D (**2**)

Figure 1. Representative nodulisporic acid congeners.

analogues not easily accessible by chemical modification of the naturally occurring indoles. The cornerstone of the proposed synthetic strategy would entail the 2-substituted indole synthesis that we introduced in 1986 and have subsequently developed.[6] To initiate this program, we selected (+)-nodulisporic acid F (**3**), the simplest congener of the nodulisporane family, as our initial target.

From the synthetic perspective, we envisioned that (+)-nodulisporic acid F could be assembled via a late-stage *B*-alkyl Suzuki−Miyaura cross-coupling[7] of pentacyclic indole **4** with methyl-(*E*)-3-bromo-2-methylpropenoate (Scheme 1). Indole **4** in turn was expected to arise via

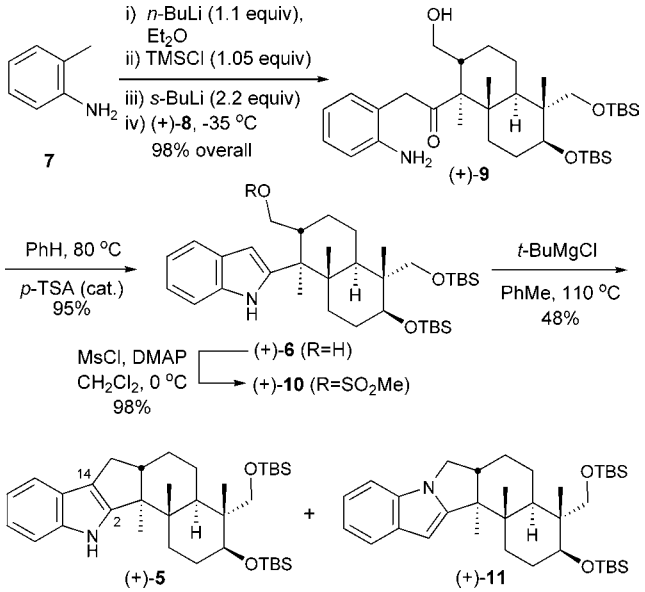
Scheme 1. First-Generation Retrosynthetic Analysis



selective removal of the primary TBS group in **5**, followed by oxidation and methylenation. Construction of ring C in **5** would then call for a regioselective intramolecular alkylation of **6**, wherein the alcohol functional group would first be transformed into a suitable leaving group. This tactic had been developed in conjunction with our 21-isopentenylpaxilline[8] synthesis. Finally, **6** would arise via union of the N-silylated dianion derived from *o*-toluidine (**7**) with known tricyclic lactone (+)-**8**.[9]

In the event, treatment of the N-silylated dianion derived in situ from *N*-trimethylsilyl-*o*-toluidine with lactone (+)-**8** furnished ketoaniline (+)-**9** in near quantitative yield (Scheme 2). The failure to undergo the expected indolization, known

Scheme 2. Access to the Pentacyclic Core of **3**



to occur in simpler systems, is attributed to steric effects exerted by the adjacent C3 (nodulisporic acid numbering) quaternary center, which is thought to attenuate the rate of the requisite heteroatom−Peterson olefination relative to the thermodynamically driven intramolecular N → O silyl migration. Pleasingly, acid-catalyzed cyclodehydration furnished indole (+)-**6** in 95% yield, which was then readily converted to the corresponding mesylate (+)-**10** (e.g., MsCl, DMAP; 98% yield). Turning to construction of ring C, we planned to take advantage of a previous observation in our laboratory[8] which demonstrated that indoles similar to (+)-**10** would undergo cyclization in a regioselective manner at the C3 indole position via the corresponding indolyl *N*-Grignard species, despite the inherent stereoelectronic bias favoring reaction at N1, simply by executing the reaction at elevated temperatures. Implementation of these conditions yielded a mixture (2.5:1.0) of regioisomers (+)-**5** and (+)-

(5) (a) Smith, A. B., III; Mewshaw, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 1796. (b) Mewshaw, R. E.; Taylor, M. D.; Smith, A. B., III. *J. Org. Chem.* **1989**, *54*, 3449. (c) Smith, A. B., III; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197. (d) Smith, A. B., III; Kanoh, N.; Minakawa, N.; Rainier, J. D.; Blase, F. R.; Hartz, R. A. *Org. Lett.* **1999**, *1*, 1263. (e) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *114*, 1438. (f) Smith, A. B., III; Naoki, K.; Ishiyama, H.; Minikawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 8228.

(6) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengler, P. A. *Tetrahedron* **1986**, *42*, 2957.

(7) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

(8) Smith, A. B., III; Cui, H. *Org. Lett.* **2003**, *5*, 587.

(9) Smith, A. B., III; Cho, Y. S.; Ishiyama, H. *Org. Lett.* **2001**, *3*, 3971.

11, respectively, in a combined yield of 48%. The structure of (+)-**11** was verified by X-ray crystallography (Figure 2).

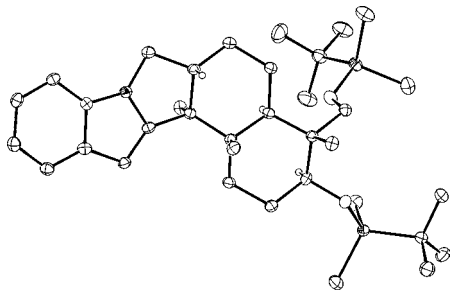
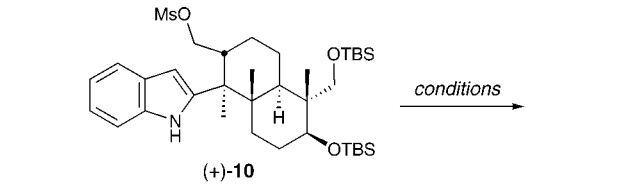


Figure 2. ORTEP representation of (+)-**11**.

Efforts to obtain suitable crystals of (+)-**5** were unfortunately complicated by decomposition, presumably via oxidative cleavage of the indole C2−C14 bond, a now well-known oxidation process of the indole diterpenes.[10]

Given the modest regioselectivity in the C-ring construction, a detailed optimization study was undertaken (Table 1). Best results were obtained when $Zn(OTf)_2$ was added to

Table 1. Optimization of C-Ring Closure

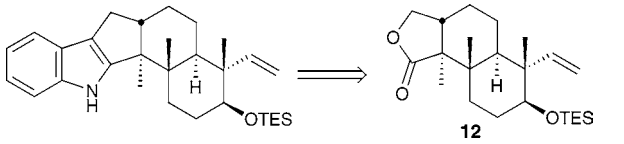


conditions	ratio **5:11**	yield
t-BuMgCl, PhMe, 23 °C	1.0:8.2	
t-BuMgCl, PhMe, 110 °C	2.5:1.0	48%
Bu_2Mg, PhMe, 110 °C	2.8:1.0	42%
$Mg(HMDS)_2$, PhMe, 110 °C	1.0:1.8	21%
MeMgI, PhMe, 110 °C	7.7:1.0	41%
t-BuMgCl, PhMe, $Zn(OTf)_2$ (5 equiv), 110 °C	6.3:1.0	63%
t-BuMgCl, PhMe, $Zn(OTf)_2$ (10 equiv), 110 °C	9.0:1.0	72%

the reaction mixture. For example, treatment of (+)-**10** with *t*-BuMgCl and $Zn(OTf)_2$ (10 equiv) in PhMe at 110 °C furnished (+)-**5** in 72% isolated yield, accompanied only by a minor amount of (+)-**11** (ca. 7%). Presumably, this reaction proceeds via in situ transmetalation of the initially formed indolyl *N*-Grignard to the more highly covalent indolyl *N*-zinc species.[11] Despite these favorable results, further advancement of pentacyclic indole (+)-**5** toward (+)-nodulisporic acid F was thwarted by our inability to effect selective removal of the primary TBS group in the presence of the C7 secondary TBS ether. Although frustrating, this result was not entirely unexpected given the neopentyl nature of the targeted primary TBS ether. From the perspective of the ultimate goal of defining a modular synthetic strategy, that might be generally applicable to other members of the class of nodulisporanes and analogues thereof, this result had important implications on the design of an endgame sequence.

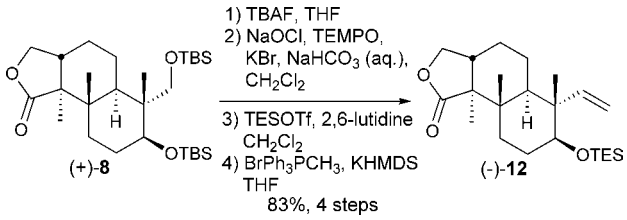
A revised strategy was therefore put forth (Scheme 3), wherein the originally planned late-stage modifications of the eastern portion of lactone (+)-**8** (Scheme 1) would be executed prior to union. The requisite lactone (−)-**12** was prepared via a four-step sequence from (+)-**8** (Scheme 4)

Scheme 3. A Second-Generation Synthetic Strategy



comprising a fluoride-induced desilylation, followed by selective oxidation of the resulting primary alcohol with TEMPO/NaOCl under biphasic conditions[12] to yield the corresponding hydroxyaldehyde. Protection of the C7 hydroxyl group as the TES ether and Wittig methylenation furnished (−)-**12**; the overall yield was 83%.

Scheme 4. Preparation of Lactone (−)-**12**



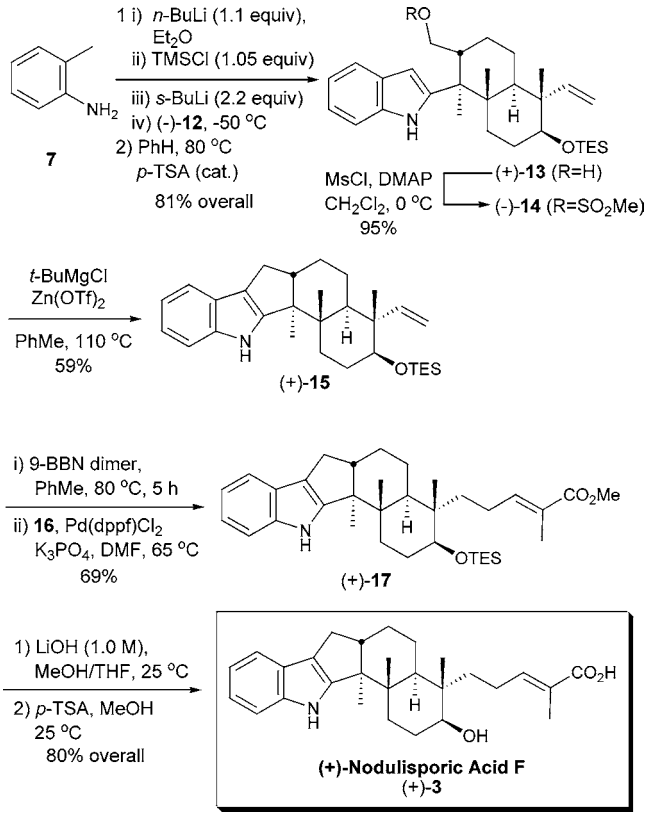
As expected, lactone (−)-**12** served as a competent coupling partner when exposed to the N-silylated dianion derived in situ from *N*-trimethylsilyl-*o*-toluidine; the resultant ketoaniline (85% yield) was then subjected to acid-promoted cyclodehydration to provide indole (+)-**13** in 81% overall yield for the two steps (Scheme 5). Conversion to the corresponding mesylate (−)-**14** (95% yield), followed by application of our now optimized conditions for construction of ring C, returned pentacyclic indole (+)-**15** in 59% yield, accompanied by the N1 regioisomer in ca. 8% yield.

(10) Sings, H.; Singh, S. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier Academic Press: New York, 2003; Vol. 60, p 51.

(11) Bergman, J.; Venamalm, L. *Tetrahedron* **1990**, *46*, 6061.

(12) de Nooy, A. E. J.; Basemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.

Scheme 5. Total Synthesis of (+)-Nodulisporic Acid F



At this juncture, all that remained to complete the synthesis of (+)-nodulisporic acid F was elaboration of the acid side chain via the proposed Suzuki−Miyaura cross-coupling. Despite initial difficulties to transform (+)-**15** to the corresponding 9-BBN alkylborane, presumably due to the sterically encumbered nature of the olefin, efficient conversion was eventually achieved exploiting the crystalline 9-BBN dimer in toluene at 80 °C, a protocol introduced by Johnson.[13] Subsequent solvent exchange to DMF, followed by exposure to methyl-(*E*)-3-bromo-2-methylpropenoate (**16**)[14] employing the Suzuki−Miyaura coupling conditions, furnished (+)-**17** in 69% yield.

(13) Sabat, M.; Johnson, C. *Org. Lett.* **2000**, *2*, 1089.

Having now achieved construction of the carbon framework of nodulisporic acid F, saponification of methyl ester (+)-**17** to reveal the alkenoic acid side chain (87% yield) and solvolytic removal of the TES protecting group completed construction of (+)-nodulisporic acid F (92% yield), identical in all respects [e.g., 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, λ_{max}, HRMS, optical rotation, and TLC (three solvent systems)] to that of natural (+)-nodulisporic acid F [(+)-**3**].

In summary, the first total synthesis of a member of the nodulisporic acid family of ectoparasiticidal agents has been achieved. Highlights of the effective synthetic strategy include implementation of our 2-substituted indole synthesis, optimization of the regioselective cyclizations of mesylates (+)-**10** and (−)-**14** to effect installation of ring C thereby securing the pentacyclic core, and application of the *B*-alkyl Suzuki−Miyaura cross-coupling reaction to elaborate the requisite alkenoic acid side chain. Importantly, the modularity of this strategy holds promise for application to other members of the nodulisporic acid family. Work toward this end continues in our laboratory.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds, as well as selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The acid was prepared according to Dzierba, C. D.; Zandi, K. S.; Mollers, T.; Shea, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 4711.